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Drifting Too Far From Shore: Paternal Valproate Statement by the European Medicines Agency (EMA)

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On January 26th, 2024, the European Medicines Agency (EMA) issued a statement "*Precautionary measures to address potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines*" [1]. The Summary of Product Characteristics (SmPC) will be updated with explicit recommendations on advice to physicians and patients. The statement release follows a Co-ordination Group for Mutual Recognition and Decentralised Procedures—Human (CMdH) adoption of the Pharmacovigilance Risk Assessment Committee (PRAC) assessment of an underlying report from a third-party commercial entity [2].

The Scientific Committee of The European Network of Teratology Information Services (ENTIS), is concerned with the lack of data transparency supporting the decision.

In the EMA statement, the underlying registry-based study is summarily referenced. However, details relating to study methodology and analysis were unpublished and unavailable at the time of the release of the statement. This study comprises a population-based retrospective cohort using secondary data from national registries from three Nordic countries studying "neurodevelopmental disorders." Specific outcomes are not explicitly reported but cover: "*autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders and movement disorders in childhood*." The analysis "*...resulted in a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09–2.07) for neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception compared with lamotrigine or levetiracetam. The adjusted cumulative risk of neurodevelopmental disorders was estimated to be around 5% in the valproate group versus around 3% in the lamotrigine and levetiracetam group.*"

The published conclusion to the PRAC assessment of the limitations of this study seem inconsistent with the decision to issue precautionary measures:

> The study data on male patients had limitations, including differences between the groups in the conditions for which the medicines were used and in follow-up times. The PRAC could therefore not establish whether the increased occurrence of these disorders suggested by the study was due to valproate use. In addition, the study was not large enough

All authors are members of the Scientific Committee for The European Network of Teratology Information Services (ENTIS).

Summary

- Transparency is pivotal to trust between clinicians, academics, and regulatory authorities.
- Data and methodology supporting regulatory decisions must be made publicly available.
- Measurements of neurodevelopmental outcomes are complex and controversial.
- Data on paternal exposure to valproate are insufficient to warrant far-reaching precautions.
- Regulatory, academic, and clinical collaboration is essential to communicate risk.

> to identify which types of neurodevelopmental disorders children could be at increased risk of developing. Nonetheless, the Committee considered precautionary measures were warranted to inform patients and healthcare professionals.

The issue of childhood neurodevelopment following in utero exposure, and much less pre-conception paternal use, is both complex and, to some extent, controversial. Specifically, the measurement of outcomes and how to account for covariates and confounders is extremely challenging [3]. It is unfortunate that organizations such as ENTIS and other stakeholders are unable to independently assess the specific methodology applied, nor access the analytical data set, to evaluate the extent to which the study implements such considerations. This lack of methodological transparency fundamentally compromises the synthesis of an informed opinion and, consequently, how much weight such study should carry in everyday clinical practice.

We encourage the EMA and PRAC to pursue, in principle as in practice, full transparency of study methodology and analytical data supporting regulatory decisions and recommendations. Such are essential to healthcare providers and patients to support shared decision making. This is particularly important for recommendations within controversial and complex domains.

ENTIS is eager to actively participate in regulatory processes to improve safety and support effective use of medications before conception and during pregnancy/lactation. The diverse expertise in methodology and clinical fields within the ENTIS network offers the opportunity to ensure a high degree of alignment, legitimacy, and uptake of regulatory recommendations in everyday clinical practice.

Conflicts of Interest

The authors declare no conflicts of interest.

References

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